

**What is claimed is:**

1. An isolated nucleic acid molecule encoding a p75<sup>NTR</sup>-associated cell death executor.
2. The isolated DNA molecule of claim 1.
3. The isolated cDNA molecule of claim 2.
4. The isolated RNA molecule of claim 1.
5. The isolated nucleic acid molecule of claims 1-4 encoding a neurotrophin associated cell death executor protein.
6. The isolated nucleic acid molecule of claims 1-4 which comprises a sequence of AATTG TCTAC GCATC CTTAT GGGGG AGCTG TCTAA C.
7. The isolated nucleic acid molecule of claim 5 which comprises a sequence of AATTG TCTAC GCATC CTTAT GGGGG AGCTG TCTAA C.
8. The isolated nucleic acid of claim 1 operatively linked to a promoter of RNA transcription.
9. A vector which comprises the isolated nucleic acid of claim 1, operatively linked to a promoter of RNA transcription.
10. The vector of claim 9, wherein the vector is plasmid.
11. The isolated nucleic acid molecule of claim 3, wherein the nucleic acid molecule encodes human or mouse polypeptide capable of binding p75<sup>NTR</sup> receptor.
12. The isolated nucleic acid molecule of claim 11, wherein the nucleic acid molecule encodes a polypeptide capable of binding

p75<sup>NTR</sup> receptor set forth in Figure 1G-1 (SEQ ID NO: 55).

13. The isolated nucleic acid molecule of claim 3, wherein the nucleic acid molecule encodes a polypeptide capable of binding p75<sup>NTR</sup> receptor.
14. The isolated nucleic acid molecule of claim 9 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is mouse, rat or human protein.
15. The isolated nucleic acid of claim 3 which comprises the nucleic acid sequence set forth in Figure 1G-1 (SEQ ID NO: 55).
16. A host cell comprising the vector comprising the nucleic acid molecule of claim 1.
17. The host cell of claim 16, wherein the cell is selected from a group consisting of a bacterial cell, a plant cell, an insect cell, and a mammalian cell.
18. A method of producing a polypeptide capable of binding p75<sup>NTR</sup> receptor which comprises growing the host cells of claim 17 under suitable conditions permitting production of the polypeptide.
19. The method of claim 18 further comprising recovering the produced polypeptide.
20. An isolated nucleic acid molecule of at least 15 contiguous nucleotides capable of specifically hybridizing with a unique sequence included within the sequence of the nucleic acid molecule of claim 1.
21. The isolated nucleic acid of claim 20 which is a DNA molecule.

22. The isolated nucleic acid of claim 20 which is a RNA molecule.

23. An isolated nucleic acid molecule capable of specifically hybridizing with a unique sequence included within the sequence of a nucleic acid molecule which is complementary to the nucleic acid molecule of claim 1.

24. The isolated nucleic acid of claim 23 which is a DNA molecule.

25. The isolated nucleic acid of claim 23 which is a RNA molecule.

26. An antisense oligonucleotide having a nucleic acid sequence capable of specifically hybridizing to an mRNA molecule encoding a polypeptide capable of binding p75<sup>NTR</sup> receptor.

27. The antisense oligonucleotide having a nucleic acid sequence capable of specifically hybridizing to the cDNA molecule of claim 3.

28. The antisense oligonucleotide having a nucleic acid sequence capable of specifically hybridizing to the RNA molecule of claim 4.

29. A purified p75<sup>NTR</sup>-associated cell death executor.

30. A purified polypeptide capable of binding p75<sup>NTR</sup> receptor encoded by the isolated nucleic acid of claim 1.

31. A purified unique polypeptide fragment of the polypeptide capable of binding p75<sup>NTR</sup> receptor of claim 30.

32. The polypeptide capable of binding p75<sup>NTR</sup> receptor of claim 30 having substantially the same amino acid sequence as set forth in Figure 1G-1 (SEQ ID NO:55).

33. The polypeptide capable of binding p75<sup>NTR</sup> receptor of claim 30 having the amino acid sequence as set forth in Figure 1G-1 (SEQ ID NO:55).
- 5 34. The polypeptide capable of binding p75<sup>NTR</sup> receptor of claim 33 which is a vertebrate polypeptide capable of binding p75<sup>NTR</sup> receptor.
- 10 35. The polypeptide of claims 29-34 which comprises a neurotrophin associated cell death executor protein.
36. The polypeptide of claims 29-34 which comprises an amino acid sequence of NCLRILMGELSN.
- 15 37. The polypeptide of claim 35 which comprises an amino acid sequence of NCLRILMGELSN.
- 20 38. The vertebrate polypeptide capable of binding p75<sup>NTR</sup> receptor of claim 34 which is a mouse, rat, or human polypeptide capable of binding p75<sup>NTR</sup> receptor.
39. A monoclonal antibody directed to an epitope of a polypeptide capable of binding p75<sup>NTR</sup> receptor of claim 35.
- 25 40. A monoclonal antibody of claim 33 directed to a mouse, rat or human polypeptide capable of binding p75<sup>NTR</sup> receptor.
- 30 41. A polyclonal antibody directed to an epitope of the polypeptide capable of binding p75<sup>NTR</sup> receptor of claim 32.
42. A polyclonal antibody of claim 41 directed to a mouse, rat or human polypeptide capable of binding p75<sup>NTR</sup> receptor.
- 35 43. A method of inducing apoptosis in cells which comprises expressing a polypeptide capable of binding p75<sup>NTR</sup> receptor in

the cells.

5       44. A method of inducing apoptosis in a subject which comprises  
expressing a polypeptide capable of binding p75<sup>NTR</sup> receptor in  
a subject.

45. The method of claim 44 where the subject is a rat, mouse or  
human.

10       46. A transgenic nonhuman mammal which comprises an isolated DNA  
molecule of claim 2.

15       47. The transgenic nonhuman mammal of claim 46, wherein the DNA  
encoding a polypeptide capable of binding p75<sup>NTR</sup> receptor is  
operatively linked to tissue specific regulatory elements.

20       48. A method of determining physiological effects of expressing  
varying levels of a polypeptide capable of binding p75<sup>NTR</sup>  
receptor in a transgenic nonhuman mammal which comprises  
producing a panel of transgenic non human mammal expressing a  
different amount of polypeptide capable of binding p75<sup>NTR</sup>  
receptor.

25       49. A method of producing a p75<sup>NTR</sup>-associated cell death executor  
which comprises:

- 30       (a) inserting a nucleic acid molecule encoding the p75<sup>NTR</sup>-  
associated cell death executor into a suitable vector;  
(b) introducing the resulting vector into a suitable host  
cell;  
(c) selecting the introduced host cell for the expression of  
the p75<sup>NTR</sup>-associated cell death executor;  
(d) culturing the selected cell to produce the p75<sup>NTR</sup>-  
associated cell death executor; and  
35       (e) recovering the p75<sup>NTR</sup>-associated cell death executor  
produced.

50. A method of inducing apoptosis of cells in a subject comprising administering to the subject a purified polypeptide capable of binding p75<sup>NTR</sup> receptor in an amount effective to induce apoptosis.

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51. The method of claim 50 wherein the subject is a mammal.

52. The method of claim 51, wherein the mammal is mouse, rat or human.

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53. A pharmaceutical composition comprising a purified polypeptide capable of binding p75<sup>NTR</sup> receptor of either claim 32 or 33 and a pharmaceutically acceptable carrier.

15 54. A pharmaceutical composition comprising an effective amount of a purified polypeptide capable of binding p75<sup>NTR</sup> receptor of either claim 32 or 33 and a pharmaceutically acceptable carrier.

20 55. A method of identifying a compound capable of inhibiting binding between p75<sup>NTR</sup> receptor and a polypeptide capable of binding p75<sup>NTR</sup> receptor comprising:

- 25 a) contacting the compound with the polypeptide capable of binding to p75<sup>NTR</sup> receptor under conditions permitting the binding of the polypeptide capable of binding to p75<sup>NTR</sup> receptor and p75<sup>NTR</sup> receptor to form a complex;
- b) contacting the p75<sup>NTR</sup> receptor with the mixture from step a); and
- 30 c) measuring the amount of the formed complexes or the unbound p75<sup>NTR</sup> receptor or the unbound polypeptide or any combination thereof.

35 56. A method of identifying a compound capable of inhibiting binding between p75<sup>NTR</sup> receptor and a polypeptide capable of binding p75<sup>NTR</sup> receptor, where said binding forms a complex

between p75<sup>NTR</sup> receptor and a polypeptide capable of binding p75<sup>NTR</sup> receptor, comprising:

- a) contacting the compound with the p75<sup>NTR</sup> receptor under conditions permitting the binding of the polypeptide capable of binding to p75<sup>NTR</sup> receptor and p75<sup>NTR</sup> receptor to form a complex;
- b) contacting the p75<sup>NTR</sup> receptor with the mixture from step a); and
- c) measuring the amount of the formed complexes or the unbound p75<sup>NTR</sup> receptor or the unbound polypeptide or any combination thereof.

57. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a neurotrophin associated cell death executor.

58. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a human HGR74 protein.

59. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a musnade3a sequence as defined on Figure 1H.

60. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a hunade3a1 sequence as defined on Figure 1H.

61. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a hunade3a2 sequence as defined on Figure 1H.

62. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a ratnad3a sequence as defined on Figure 1H.

63. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a ratnad3b sequence as defined on Figure 1H.

5 64. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a musnade3b sequence as defined on Figure 1H.

10 65. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a humnadel sequence as defined on Figure 1H.

15 66. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a ratnadel sequence as defined on Figure 1H.

20 67. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a musnadel sequence as defined on Figure 1H.

68. The method of claims 55 or 56 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a humnade2 sequence as defined on Figure 1H.

25 69. A method for identifying an apoptosis inducing compound comprising:

- a) contacting a subject with an appropriate amount of the compound; and
- b) measuring the expression level of a polypeptide capable of binding p75<sup>NTR</sup> receptor gene and p75<sup>NTR</sup> gene in the subject, an increase of the expression levels of a polypeptide capable of binding p75<sup>NTR</sup> receptor gene and p75<sup>NTR</sup> gene indicating that the compound is an apoptosis inducing compound.



70. The method of claim 69 wherein the subject is a mammal.

71. The method of claim 70, wherein the mammal is mouse, rat or human.

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72. A method for identifying an apoptosis inducing compound comprising:

a) contacting a cell with an appropriate amount of the compound; and

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b) measuring the expression level of a polypeptide capable of binding a p75<sup>NTR</sup> receptor gene and p75<sup>NTR</sup> gene in the cell, an increase of the expression levels of polypeptide capable of binding p75<sup>NTR</sup> receptor gene and p75<sup>NTR</sup> gene indicating that the compound is an apoptosis inducing compound.

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73. A method for screening cDNA libraries of a polypeptide capable of binding p75<sup>NTR</sup> receptor using a yeast two-hybrid system using a p75<sup>NTR</sup> intracellular domain as a target.

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74. The method of claim 73 where the cDNA library is mammalian.

75. The method of claim 74 where the mammalian cDNA library is derived from rat, mouse or human cDNA libraries.

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76. The method of claim 73 where the p75<sup>NTR</sup> intracellular domain target is mammalian.

77. The method of claim 76 where the mammalian p75<sup>NTR</sup> intracellular domain target is a rat, mouse or human p75<sup>NTR</sup> intracellular domain target.

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78. A method to induce caspase-2 and caspase-3 activity to cleave poly (ADP-ribose) polymerase and fragment nuclear DNA in a cell by co-expression of polypeptide capable of binding p75<sup>NTR</sup>

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receptor and p75<sup>NTR</sup>.

79. A method to inhibit NF- $\kappa$ B activation in a cell with polypeptide capable of binding p75<sup>NTR</sup> receptor and p75<sup>NTR</sup>.

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80. A method to detect a neurodegenerative disease in a subject by detecting expression levels of a polypeptide capable of binding p75<sup>NTR</sup> receptor and p75<sup>NTR</sup>.

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81. The method of claim 80 wherein the subject is a mammal.

82. The method of claim 81, wherein the mammal is mouse, rat or human.

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83. A transgenic nonhuman mammal which comprises an isolated nucleic acid, encoding a human HGR74 protein, which is a DNA molecule.

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84. The transgenic nonhuman mammal of claim 83 where the DNA encoding a human HGR74 protein is operatively linked to tissue specific regulatory elements.

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85. A method of determining physiological effects of expressing varying levels of human HGR74 in a transgenic nonhuman mammal which comprises producing a panel of transgenic non human mammal expressing a different amount of human HGR74 protein.

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86. A method of producing human HGR74 protein into a suitable vector which comprises:

(a) inserting a nucleic acid molecule encoding a human HGR74 protein into a suitable vector;

(b) introducing the resulting vector into a suitable host cell;

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(c) selecting the introduced host cell for the expression of the human HGR74 protein;

- (d) culturing the selected cell to produce the human HGR74 protein; and
- (e) recovering the human HGR74 protein produced.

- 5      87. A method of inducing apoptosis of cells in a subject comprising administering to the subject the purified human HGR74 protein in an amount effective to induce apoptosis.
- 10      88. The method of claim 86 wherein the subject is a mammal.
- 15      89. The method of claim 87, wherein the mammal is mouse, rat or human.
- 20      90. A pharmaceutical composition comprising a purified human HGR74 protein and a pharmaceutically acceptable carrier.
- 25      91. A method for identifying an apoptosis inducing compound comprising:
  - (a) contacting a subject with an appropriate amount of the compound; and
  - (b) measuring the expression level of human HGR74 protein gene and p75<sup>NTR</sup> gene in the subject, an increase of the expression levels of human HGR74 protein and p75<sup>NTR</sup> gene indicating that the compound is an apoptosis inducing compound.
- 30      92. The method of claim 91 wherein the subject is a mammal.
- 35      93. The method of claim 92, wherein the mammal is mouse, rat or human.
- 40      94. A method for identifying an apoptosis inducing compound comprising:
  - (a) contacting a cell with an appropriate amount of the

compound; and

- (b) measuring the expression level of human HGR74 protein gene and p75<sup>NTR</sup> gene in the cell, an increase of the expression levels of human HGR74 protein gene and p75<sup>NTR</sup> gene indicating that the compound is an apoptosis inducing compound.

95. A method for screening cDNA libraries human HGR74 protein using a yeast two-hybrid system using a p75<sup>NTR</sup> intracellular domain as a target.

96. The method of claim 95 where the cDNA library is mammalian.

97. The method of claim 96 where the mammalian cDNA library is derived from rat, mouse or human cDNA libraries.

98. The method of claim 95 where the p75<sup>NTR</sup> intracellular domain target is mammalian.

99. The method of claim 98 where the mammalian p75<sup>NTR</sup> intracellular domain target is a rat, mouse or human p75<sup>NTR</sup> intracellular domain target.

100. A method to induce caspase-2 and caspase-3 activity to cleave poly (ADP-ribose) polymerase and fragment nuclear DNA in a cell by co-expression of human HGR74 protein and p75<sup>NTR</sup>.

101. A method to inhibit NF- $\kappa$ B activation in a cell with human HGR74 protein and p75<sup>NTR</sup>.

102. A method to detect a neurodegenerative disease in a subject by detecting expression levels of human HGR74 protein and p75<sup>NTR</sup>.

103. The method of claim 102 wherein the subject is a mammal.

104. The method of claim 103, wherein the mammal is human.

105. A method of identifying a compound, which is an apoptosis inhibitor, said compound is capable of inhibiting specific binding between polypeptide capable of binding p75<sup>NTR</sup> receptor and p75<sup>NTR</sup> receptor, so as to prevent apoptosis which comprises:

(a) contacting the polypeptide capable of binding p75<sup>NTR</sup> receptor with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace a polypeptide capable of binding p75<sup>NTR</sup> receptor and the p75<sup>NTR</sup> receptor and the bound p75<sup>NTR</sup> receptor to form a complex; and

(b) detecting the displaced polypeptide capable of binding p75<sup>NTR</sup> receptor or the complex formed in step (a), wherein the displacement indicates that the compound is capable of inhibiting specific binding between the polypeptide capable of binding p75<sup>NTR</sup> receptor and the p75<sup>NTR</sup> receptor.

106. The method of claim 105, wherein the inhibition of specific binding between the polypeptide capable of binding p75<sup>NTR</sup> receptor and the p75<sup>NTR</sup> receptor affects the transcription activity of a reporter gene.

107. The method of claim 106, where in step (b) the displaced polypeptide capable of binding p75<sup>NTR</sup> receptor or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the polypeptide capable of binding p75<sup>NTR</sup> receptor and the p75<sup>NTR</sup> receptor is inhibited and

the polypeptide capable of binding p75<sup>NTR</sup> receptor is displaced.

5 108. The method of claim 105, wherein the p75<sup>NTR</sup> receptor is bound to a solid support.

109. The method of claim 105, wherein the compound is bound to a solid support.

10 110. The method of claim 105, wherein the compound comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

15 111. The method of claim 105 wherein the contacting of step (a) is in vitro.

112. The method of claim 105, wherein the contacting of step (a) is in vivo.

20 113. The method of claim 112, wherein the contacting of step (a) is in a yeast cell.

25 114. The method of claim 112, wherein the contacting or step (a) is in a mammalian cell.

115. The method of claim 105, wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a cell surface receptor.

30 116. The method of claim 112, wherein the cell-surface receptor is the p75 receptor.

117. The method of claim 105 where in the polypeptide capable of

binding p75<sup>NTR</sup> receptor is a neurotrophin associated cell death  
exectuor.

5 118. The method of claim 105 where in the polypeptide capable of  
binding p75<sup>NTR</sup> receptor is a human HGR74 protein.

119. The method of claim 105 wherein the polypeptide capable of  
binding p75<sup>NTR</sup> receptor is a neurotrophin associated cell death  
executor.

10 120. The method of claim 105 wherein the polypeptide capable of  
binding p75<sup>NTR</sup> receptor is a human HGR74 protein.

15 121. The method of claim 105 wherein the polypeptide capable of  
binding p75<sup>NTR</sup> receptor is a musnade3a sequence as defined on  
Figure 1H.

20 122. The method of claim 105 wherein the polypeptide capable of  
binding p75<sup>NTR</sup> receptor is a hunade3a1 sequence as defined on  
Figure 1H.

25 123. The method of claim 105 wherein the polypeptide capable of  
binding p75<sup>NTR</sup> receptor is a hunade3a2 sequence as defined on  
Figure 1H.

124. The method of claim 105 wherein the polypeptide capable of  
binding p75<sup>NTR</sup> receptor is a ratnad3a sequence as defined on  
Figure 1H.

30 125. The method of claim 105 wherein the polypeptide capable of  
binding p75<sup>NTR</sup> receptor is a ratnad3b sequence as defined on  
Figure 1H.

126. The method of claim 105 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a musnade3b sequence as defined on Figure 1H.

5 127. The method of claim 105 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a humnade1 sequence as defined on Figure 1H.

10 128. The method of claim 105 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a ratnade1 sequence as defined on Figure 1H.

15 129. The method of claim 105 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a musnade1 sequence as defined on Figure 1H.

20 130. The method of claim 105 wherein the polypeptide capable of binding p75<sup>NTR</sup> receptor is a humnade2 sequence as defined on Figure 1H.

25 131. An isolated nucleic acid molecule encoding a deletion mutant of a wild type polypeptide capable of binding with a p75<sup>NTR</sup> receptor, designated neurotrophin associated cell death executor protein (NADE), wherein the N-terminal 1-40 amino acids of wild type NADE polypeptide have been deleted and the deletion mutant is designated NADE N(41-124), and the NADE N(41-124) induces apoptosis in the presence of p75<sup>NTR</sup>.

30 132. An isolated nucleic acid molecule encoding a deletion mutant of a wild type polypeptide capable of binding with a p75<sup>NTR</sup> receptor, designated neurotrophin associated cell death executor protein (NADE), wherein the C-terminal 72-124 amino acids of wild type NADE polypeptide have been deleted and the



deletion mutant is designated NADE N(1-71), and the NADE N(1-71) induces apoptosis in the presence of p75<sup>NTR</sup> and in the absence of p75<sup>NTR</sup>.

- 5      133. An isolated nucleic acid molecule encoding a deletion mutant  
of a wild type polypeptide capable of binding with a p75<sup>NTR</sup>  
receptor, designated neurotrophin associated cell death  
10      executor protein (NADE), wherein the N-terminal 1-40 amino  
acids and the C-terminal 72-124 amino acids of wild type NADE  
polypeptide have been deleted and the deletion mutant is  
designated NADE N(41-71), and the NADE N(41-71) induces  
apoptosis in the presence of p75<sup>NTR</sup> and in the absence of  
p75<sup>NTR</sup>.
- 15      134. An isolated nucleic acid molecule encoding a deletion mutant  
of a wild type polypeptide capable of binding with a p75<sup>NTR</sup>  
receptor, designated neurotrophin associated cell death  
executor protein (NADE), wherein the C-terminal 121-124 amino  
20      acids of wild type NADE polypeptide have been deleted and the  
deletion mutant is designated NADE N(1-120) and the NADE N(1-  
120) induces apoptosis in the presence of p75<sup>NTR</sup>.
- 25      135. An isolated nucleic acid molecule encoding a deletion mutant  
of a wild type polypeptide capable of binding with a p75<sup>NTR</sup>  
receptor, designated neurotrophin associated cell death  
executor protein (NADE), wherein the C-terminal 113-124 amino  
acids of wild type NADE polypeptide have been deleted and the  
deletion mutant is designated NADE N(1-112) and the NADE N(1-  
112) induces apoptosis in the presence of p75<sup>NTR</sup>.
- 30      136. An isolated nucleic acid molecule encoding a deletion mutant  
of a wild type polypeptide capable of binding with a p75<sup>NTR</sup>  
receptor, designated neurotrophin associated cell death

executor protein (NADE), wherein the C-terminal 101-124 amino acids of wild type NADE polypeptide have been deleted and the deletion mutant is designated NADE N(1-100) and the NADE N(1-100) induces apoptosis in the presence of p75<sup>NTR</sup> and in the absence of p75<sup>NTR</sup>.

137. An isolated nucleic acid molecule encoding a mutation of a wild type polypeptide capable of binding with a p75<sup>NTR</sup> receptor, designated neurotrophin associated cell death executor protein (NADE), wherein the point mutation results in Ala at amino acid position 99 for Leu at amino acid position of wild type NADE polypeptide, wherein the substitution mutant polypeptide is designated NADE N(L99A) and the NADE N(L99A) induces apoptosis in the presence of p75<sup>NTR</sup>.